Remarks

Claims 1 and 3-9 are pending in the application. Claim 1 has been amended.

Applicant requests that Examiner initial and return a copy of the PTO Form 1449 which was submitted with the response to the Office Action mailed March 5, 2004.

I. Summary of the Amendment

A. Specification

The specification at page 6, line 20 has been amended to correct an obvious error wherein the chelating moiety is stated to chelate in a N_4 conformation through its "NH_2" groups. Clearly, Applicant intended to state that the N_4 chelation occurs through the "NH" groups of the tetrapeptide chelating moiety, since three of the four peptide amide nitrogen atoms are secondary amides. The terminal amino group of the tetrapeptide chelating moiety, though it is a primary amide, is reasonably construed as also containing a "NH" group. The terminal NH_2 group is reasonable understood as -NH bonded to –H (-NH-H) rather than bonded to an adjacent amino acid (NH-amino acid) as in the NH groups of the non-terminal amino acids in the tetrapeptide chelating moiety.

B. Claims

Claim 1 has been amended:

1. to remove the expression "or an analog or a peptide fragment thereof" and
2. to replace the expression, "capable of complexing with a selected radionuclide in an N_4 configuration" with the expression, "that complexes with a selected radionuclide in an N_4 configuration;" and
3. to specify that the radiolabeling moiety, M, comprises a tetrapeptide chelating moiety.

Support for (1) above is found in claim 1 as filed. Support for (2) and (3) above is found in the specification at page 6, line 19-21.

II. Response to Examiner's Objection to the Specification

The Examiner has objected to the specification, regarding an alleged typographical error at page 4, line 14, wherein the abbreviation "Ana" should be "Aba."

Amendments to the Drawings

The attached drawing sheet includes changes to Fig. 1. This sheet replaces original Fig. 1.

In amended Fig. 1, unnecessary text, erroneously introduced during prosecution, has been removed.

Attachments: Replacement Sheet

Annotated Sheet showing changes

Applicant has previously corrected this typographical error by a Preliminary Amendment included in the Response to Notice of Missing Parts under 35 U.S.C. § 371 in the United States Designated/Elected Office (hereinafter, "2001 Response"). The 2001 Response was mailed by Applicant on June 4, 2001, and docketed by the Patent Office, according to PAIR, on June 6, 2001.

The 2001 Response included additional changes which are relevant to the Examiner's present rejection of claim 1 under 35 U.S.C. § 112, 2nd paragraph. The changes made to the specification by the 2001 Response, which are relevant to the present Office Action, are listed below.

1. At page 3, line 25, the expression "H-Gly—Pro—Arg-OH" was replaced with --H-Gly—Pro—Arg-OH (SEQ ID NO:1)--.
2. At page 4, line 14, the expression "H-Gly—Pro—Arg—Pro—Pro—Ana—Gly—Gly—(D)-Ala—Gly" was replaced with --H-Gly—Pro—Arg—Pro—Pro—Aba—Gly—Gly— (D)-Ala—Gly--.
3. At page 4, line 15, the expression "(SEQ ID NO:1)" was replaced with
--(SEQ ID NO:5)--.

Please note that the change made "at page 6, line 24" by the 2001 Response was reversed by the Amendment to the Specification (replacing the paragraph beginning at page 6, line 19) requested in Applicant's response to the Office Action Dated March 5, 2004.

III. Response to Rejection under 35 U.S.C. § 102(e)

Claims 1, 3, 4 and 7-9 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Dean *et al.* The Examiner has alleged that "both Applicant and Dean *et al.* disclose compositions comprising the peptide Gly—Pro—Arg having a radiolabel binding moiety."

For a reference to anticipate a claim, every limitation of that claim must identically appear, either expressly or inherently, in the reference. *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Absence of any claim element from the reference "negates anticipation."

Kloster Speedsteel AB v. Crucible, Inc., 230 USPQ 81, 84 (Fed. Cir. 1986); *Rowe v. Dror,* 42 USPQ2d 1550, 1552 (Fed. Cir. 1992).

Claim 1 of the present invention, as amended herein, recites a structure which includes a tetrapeptide chelating moiety that complexes with a radionuclide in an N_4 configuration. Dean *et al.* does not teach a tetrapeptide chelating moiety that complexes with a radionuclide in an N_4 configuration as recited in the claims as herein amended.

Based on the herein amendment of claim 1, Applicant respectfully requests that the Examiner withdraw the rejection of claims 1-4 and 7-8 under 35 U.S.C. §102(e).

IV. Response to Rejection under 35 U.S.C. § 103(a)

Claims 1, 3, 4, 7 and 8 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dean *et al.*, in view of Kawasaki *et al.* and Laudano *et al.*

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP 706.02(j))

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully submits that the Examiner has not established that the claimed invention, recited in claim 1 as herein amended, is *prima facie* obvious over Dean *et al.*, in view of Kawasaki *et al.* and Laudano *et al.*

Dean *et al.* teach peptides that are radiolabeled by covalent binding to a Tc-99m binding moiety that is one of a group of six defined, sulfur-containing structures. Kawasaki *et al.* disclose various peptides that are analogs of the *N*-terminal portion of fibrin α-chain and which are examined for effects on fibrinogen/thrombin clotting. Laudano *et al.* disclose peptides corresponding to the amino termini of fibrin α- and β-chains, fibrinogen binding affinity of the disclosed peptides, and fibrin polymerization inhibition activity of the disclosed peptides.

The Examiner alleges that it would have been obvious to modify Dean *et al.* to generate various peptides containing Gly—Pro—Arg that bind fibrin, and to conjugate such peptides to a radiolabeling moiety.

The combination of the cited references, neither teach nor suggest the claim element of a tetrapeptide chelating moiety that complexes with a radionuclide in an N_4 configuration as recited in the claims as amended herein. Based on the herein amendment of claim 1, Applicant respectfully requests that the Examiner withdraw the rejection of claims 1, 3, 4, 7 and 8 under 35 U.S.C. §103(a).

V. Response to Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 3-9 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly ambiguous for reciting the phrase "analog or peptide fragment thereof." Claim 1 has been amended herein to remove the phrase "analog or peptide fragment thereof."

Examiner has additionally stated that there is no antecedent basis for Sequence ID No. 1 in the claims because the sequence identified in claim 1 as Sequence ID No. 1 is inconsistent with the decapeptide disclosed at page 4, lines 14-15 in the specification.

As discussed above in Section II of this Amendment, Sequence ID No. 1 in claim 1 has antecedent basis (at page 3, line 25 of the specification) as a result of the 2001 Response. Additionally, the sequence ID No. for the decapeptide disclosed at page 4, lines 14-15 was changed by the 2001 Response to Sequence ID No. 5.

Claim 1, as amended herein, is clear, definite, and in compliance with 35 U.S.C. § 112, second paragraph. Applicant respectfully requests that the rejection of claims 1 and 3-9 under 35 U.S.C. §112, second paragraph be withdrawn.

VI. Response to Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 3, 4 and 7-9 have been rejected under 35 U.S.C. § 112, first paragraph. Examiner alleges that the specification, while enabling the N_4 configuration generated from the amino acid sequence Gly—(D)-Ala—Gly—Gly, does not reasonably provide enablement for all N_4 chelating moieties.

To be enabling, a specification must teach one of ordinary skill in the art how to make and use the claimed invention without undue experimentation. However, the

specification need only enable the invention, not information previously known in the art. "A patent need not disclose what is well-known in the art." *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). "A patent need not teach, and preferably omits, what is well-known in the art." *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 U.S.P.Q.2d 1737, 1743 (Fed. Cir. 1987), cert. denied, 108 S.Ct. 346 (1987); *Hybritech, Inc. v. Monoclonal Antibodies*, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). The specification may assume "that which is common and well-known" to persons skilled in the relevant art. *Webster Loom v. Higgins*, 105 U.S. 580 (1981). Also see M.P.E.P. 601.

Applicant has amended claim 1 herein to specify that the radiolabeling moiety, M, comprises a tetrapeptide moiety which complexes a radionuclide in an N_4 configuration.

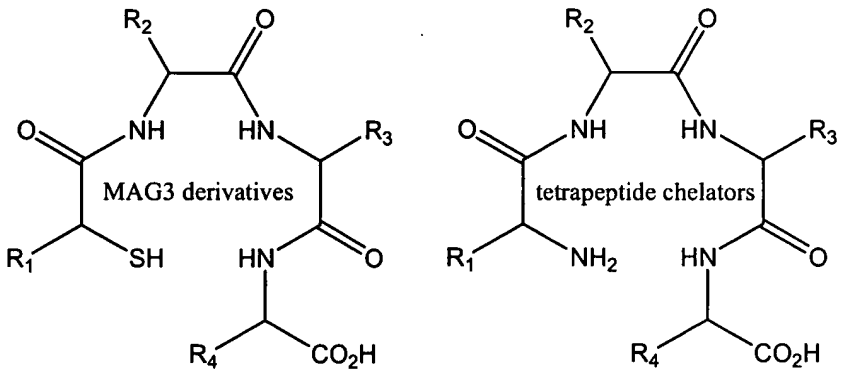
This tetrapeptide chelating moiety may be introduced into the nascent peptide of the invention synthetically as a part of the peptide synthesis, by modification of the amino acid sequence of the C-terminus region of the primary peptide. Applicant discloses, at page 7, line 17, that the peptides of the invention are prepared using a commercially available Shimadzu solid phase peptide synthesizer and purified by preparative high performance liquid chromatography using a commercially available HFIsil, C-18 chromatography column. Solid phase preparation of small peptides is a well established technology which is often fully automated. Solid phase synthesizers available to the skilled artisan are capable of preparing large numbers of peptides in either random or directed combinatorial protocols.

Applicant also clearly discloses (page 7, line 21-27) a process whereby a chelate is formed between compounds of the invention and a selected radionuclide. The incubation of compounds of the invention with a radionuclide, such as Tc-99m, and a reducing agent, such as $SnCl_2$, is a process which is highly amenable to being employed with large numbers of compounds of the invention in parallel to optimize the tetrapeptide chelating moiety for different compounds of the invention chelated to different selected radionuclides.

Likewise, applicant describes the HPLC analysis of the formed chelate (page 7, line 27-32), as employing both a UV detector and a gamma counter, to determine the degree to which the radionuclide is incorporated into the peptide. The disclosed synthesis instructions and analytical methods required to make and evaluate compounds of the invention are well within the knowledge and ability of one of ordinary skill in the art.

The Examiner states that the tetrapeptide chelating moiety is only enabled in Applicant's specification for the amino acid sequence Gly-(D)-Ala-Gly-Gly. However, Applicant's specification "need not teach, and preferably omits, what is well-known in the art." Other tetrapeptide chelating moieties are known to those of ordinary skill in the art.

An N4 chelating tetrapeptide is a peptide which is capable of binding a metal atom through coordination with four nitrogen atoms. The design, preparation, optimization and analysis of tetrapeptide moieties that chelate radionuclides in an N4 configuration is described, for example, by Vanbilloen *et al., Nucl. Med. Biol.*, 22(3) p325-38, 326 (1995), (of record). Vanbilloen *et al.* disclose tetrapeptide chelators, as depicted below, as being analogous to the MAG3 derivatives which were previously known radionuclide chelating moieties. Vanbilloen *et al.* discloses syntheses and analytical data for eleven specific examples of tetrapeptide chelators which chelate ^{99m}Tc in an N4 configuration.



The preparation of the Vanbilloen tetrapeptide chelating moieties comprises conventional solution phase peptide syntheses using conventional protecting group strategies. The analytical methods employed by Vanbilloen *et al* are common techniques which include paper chromatography and HPLC. All of the reagents and instrumentation employed by Vanbilloen *et al.* for the syntheses and analyses of tetrapeptide chelating moieties are commercially available.

Applicant has shown in the specification that compounds of the invention may be prepared by use of methodology and technology that are known to one of ordinary skill in the art of peptide synthesis. The preparation and analysis of tetrapeptide moieties other than Gly-(D)-Ala-Gly-Gly, that are capable of chelating a radionuclide in an N4 configuration is

well known and well within the capability of one of ordinary skill in the art. Vanbilloen *et al.* discloses no fewer than eleven such N4 chelating tetrapeptides. Applicant therefore submits that the claimed invention is adequately supported by the specification given the state of the art and information is readily available to one of ordinary skill in the art.

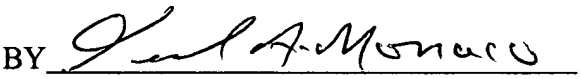
Applicant respectfully requests that the rejection of claims 1, 3, 4 and 7-9 under 35 U.S.C. § 112, first paragraph be withdrawn.

Conclusion

Applicant believes this Response and Amendment to be fully responsive to the Examiner's Office Action. Applicant submits that the claims as herein amended are novel and nonobvious over the cited art, are not indefinite, and are fully enabled. Applicant therefore respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

MADHUKAR (MATHEW) THAKUR

BY 

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